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Case report

Multiple bee stings, peritumoral mast cell degranulation and anaphylaxis – Is there a relationship?

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ABSTRACT

A case of a 58-year-old with fatal anaphylaxis due to multiple bee stings is reported. Supportive evidence for anaphylaxis included post-mortem serum tests, which demonstrated a markedly elevated tryptase level and increased sensitivity to bees on radioallergosorbent test (RAST). At autopsy a previously undiagnosed esophageal adenocarcinoma involving the gastroesophageal (GE) junction was also identified. Histology of the tumor demonstrated significant numbers of mast cells, many of which were degranulating. Increased numbers of mast cells, as in mastocytosis, are known to predispose to an allergic sensitivity to Hymenoptera. The finding of a significant peritumoral mast cell population with degranulating forms in this case, therefore, raises the possibility that death due to anaphylaxis was contributed to by mast cell proliferation in an occult esophageal carcinoma.

1. Introduction

Anaphylaxis can present a series of unique challenges to the forensic pathologist as there may be a lack of anatomic findings at autopsy.[1] A clinical history of previous allergy to stinging insects, foods or drugs may be useful, but does not necessarily exclude an anaphylactic reaction. In particular, insect allergy can develop at any age; even after a number of uneventful stings.[2] A case of anaphylaxis is reported where the deceased was also discovered to have an occult adenocarcinoma. As mast cells are central to anaphylaxis but are also a component of tumor matrix,[3] the possibility that degranulation of peritumoral mast cells contributed to death in the setting of multiple bee stings was raised.

2. Case report

A 58-year-old man was working outdoors during autumn when stung by 8 or 9 bees. The outdoor work consisted of removal and movement of logs. The temperature was in the low 30's Celsius at the time of the envenomation. In the past, he had reported no ill effects from bee stings. He departed the scene as the driver of a motor vehicle shortly thereafter. 20 min later he was followed by work colleagues who found him slumped and unresponsive in his motor vehicle further down the road. Ambulance personnel were notified and resuscitation was conducted, which included administration of epinephrine. He was not taking any regular medications. He died and a coronial autopsy was performed.

At autopsy, the external examination demonstrated appreciable swelling of the dorsum of the left hand. A bee sting was removed from the nape of his neck. No other external stings were visualized. There were no rashes. Internal examination demonstrated no appreciable laryngeal edema. The heart weighed 452 g and showed left ventricular hypertrophy. Minimal atherosclerosis was apparent. The lungs demonstrated pulmonary edema and weighed 1769 g combined.

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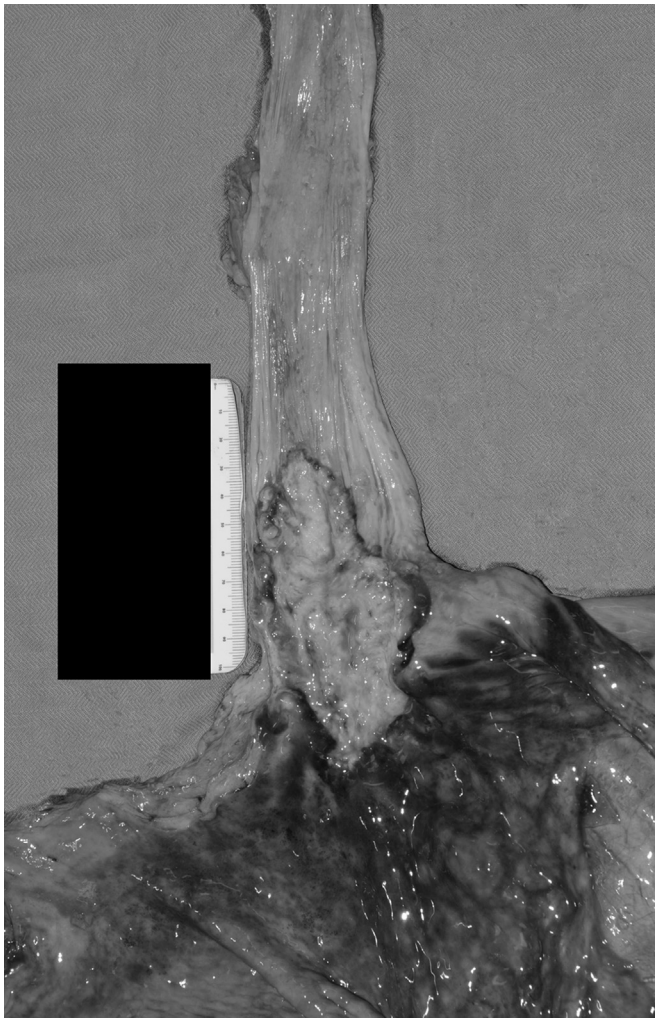

Fig. 1. Macroscopic image. Note the tumor located in the distal esophagus and also involving the gastroesophageal junction.

There was no hepatomegaly. The spleen was slightly enlarged at 292 g, but was otherwise structurally normal without lesions.

Unexpectedly and previously undiagnosed within the distal esophagus and involving the gastroesophageal junction was a large adenocarcinoma (Fig. 1). The tumor measured 12 cm × 6 cm and invaded to a depth of 1.5 cm. The tumor grossly approached the serosa of the stomach and external surface of the esophagus, but without perforation of these structures. One enlarged paraesophageal lymph node was sampled but found to be negative for adenocarcinoma. The stomach mucosa demonstrated autolysis.

Post-mortem serum was sent for evaluation. The autopsy was performed two days after his death, but serum was obtained the day prior, upon admission to the mortuary approximately 24 h after his death. The serum was sourced from femoral blood. Post-mortem laboratory data showed an elevated mast cell tryptase >200 μg/L (normal < 12 μg/L), total IgE 330 kU/L (normal < 110 kU/L) and a radioallergosorbent test (RAST) bee specific IgE score of 2 kU/L (normal < 0.35 kU/L). The laboratory evaluation was performed using CAP assays. A specimen of post-mortem peripheral blood analyzed by toxicology showed no alcohol, common drugs or drugs of abuse.

The tumor features were diagnostic of moderately differentiated adenocarcinoma with tumor associated necrosis. Microscopically, the tumor invaded the muscularis propria into the periesophageal soft tissues (adventitia). At the invasive border of the tumor was marked chronic inflammation, including numerous

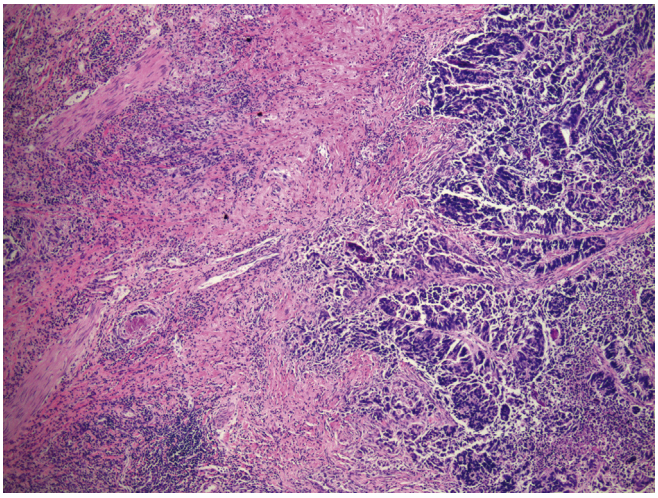

Fig. 2. Low power microscopic image (Hematoxylin and Eosin stain). Note the adenocarcinoma at the right side of the field. At the left is a dense inflammatory infiltrate.

mast cells (Fig. 2). A toluidine blue stain was performed to ascertain mast cell density (Fig. 3) and to reveal any evidence of degranulation (Fig. 4).

3. Discussion

Elevated tryptase is strong evidence of anaphylaxis in combination with the circumstances in this case. Additionally there was sensitivity to bee stings given a bee specific IgE score of 2.0 kU/L. The cause of death was, therefore, anaphylaxis due to bee stings. In suspected anaphylactic death, blood for tryptase measurements should be obtained from the femoral vessels as opposed to the heart[4] as heart blood tryptase level is elevated in a greater percentage of post-mortem controls compared to femoral blood tryptase.[4] Serum tryptase levels have also been noted to increase proportionally with the post-mortem interval.[5]

Anaphylaxis is a systemic reaction involving multiple organ systems, which may lead to death.[6] Events leading to anaphylaxis include crosslinking of IgE and aggregation of high affinity

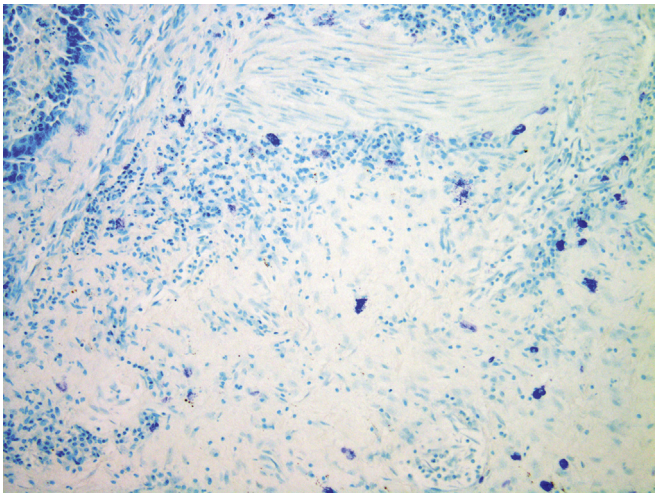

Fig. 3. High power microscopic image (Toluidine Blue stain). Note the malignant gland at the top left of the field. At the mid and lower right of the field note the mast cells with blue-purple granules. Some of the forms show dispersed granules. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

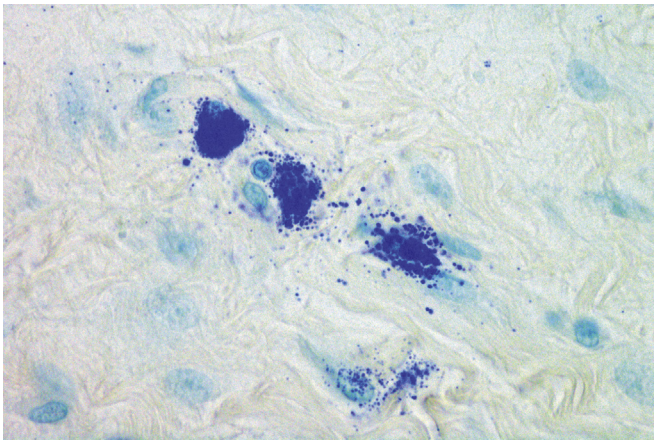

Fig. 4. High power microscopic image (Toluidine Blue stain). Mast cells are seen with some dispersed granules. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

receptors for IgE (FCε) upon exposure to allergens. This will lead to activation of mast cells and basophils and to the release of multiple mediators from granules including histamine, tryptase and many other substances. It has been noted that many compounds of Hymenoptera venom can induce FCε receptor − independent mast cell degranulation.[7] The order Hymenoptera includes bees, vespids (yellow jackets, hornets, wasps) and stinging ants.[2] Not all cases of anaphylaxis will be IgE-mediated with other mechanisms that can be non-IgE mediated, "toxic" mast cell mediator release[2,8] especially in mast cell disorders.[9] There is a much higher prevalence of anaphylaxis in mastocytosis compared to the general population.[9]

Clinical manifestations of anaphylaxis in severe reactions can include angioedema, upper airway obstruction due to laryngeal edema, bronchospasm, shock and respiratory and/or cardiac arrest among others.[1] In deaths occurring due to anaphylaxis there may be no specific macroscopic findings.[1,10] The paucity of macroscopic findings may reflect the rapid nature of the death and the absence of findings should not exclude the diagnosis of anaphylaxis.[1] In this case the specific IgE to bee venom was raised at 2.0 kU/L. However, the degree of sensitivity on skin testing or in vitro does not reliably predict the severity of a sting reaction.[2] That the deceased had reported being stung by multiple bees is significant because there may be a greater chance of systemic reaction if there are numerous stings at one time.[2]

In this case there was no microscopic evidence of Barrett's esophagus, a known precursor condition to adenocarcinoma of the esophagus. Esophageal adenocarcinoma and Barrett's esophagus of themselves may lead to complications such as hemorrhage, perforation, fistula formation or upper airway occlusion and sudden death.[11,12] There was no evidence of any primary complications from the cancer such as perforation or fistula formation.

Mast cells are known to reside in the stroma matrix of different tumors, including ovarian, gastric, esophageal, and endometrial tumors.[13–17] Elpek et al. reviewed squamous cell carcinomas of the esophagus and suggested that mast cell density may have a role in angiogenesis and account for more aggressive behavior.[13] Likewise, Ribatti et al. reported that mast cell density correlates with angiogenesis and progression in gastric carcinoma.[14] However, Tinge et al reported that mast cells are not related to prognosis in esophageal squamous cell carcinoma.[15]

The condition mastocytosis is defined by the World Health Organization (WHO) as a proliferation of mast cells and their subsequent accumulation in one or more organ systems.[18] The major categories include cutaneous, systemic mastocytosis and extracutaneous mast cell tumors.[18] Cutaneous mastocytosis includes urticaria pigmentosa and maculopapular cutaneous mastocytosis. Major criteria for systemic mastocytosis include the finding of multifocal, dense infiltrates of mast cells (15 or more in aggregates) detected in sections of bone marrow and/or extracutaneous organ(s), and confirmed by tryptase immunohistochemistry or other special stains. Minor criteria include spindle or atypical morphology of mast cells in more than 25% of mast cells, detection of KIT mutation, co-expression of CD117 with CD2 and/or CD 25 and persistent serum tryptase elevated >20 ng/ml. Immunohistochemistry was performed in this case and showed the peritumoral mast cells to express CD117 but without any co-expression. There was no mast cell infiltration of other organs.

The association between Hymenoptera venom allergy and mastocytosis seems to be more specific than for those with a food or drug induced systemic reaction.[19] In fact it has been recommended that patients with unexplained hypotension after Hymenoptera stings should undergo evaluation for major or minor criteria of systemic mastocytosis.[20]

In this case the individual died from anaphylaxis due to bee stings. While the anaphylactic process may have occurred completely independently of the tumor it is possible that the tumor may have acted as a mast cell reservoir resulting in massive degranulation upon exposure to allergens and/or through the direct effects of venom. Although there are no reports of this in the literature supportive evidence includes the microscopic finding of degranulation of many of the mast cells. However, other factors may have likewise also contributed to the mechanism of death in this case, such as posture. Whilst seated in the vehicle, the upright posture likely contributed to the severity of the shock. There is some evidence that upright posture may quickly lead to intravascular depletion in the setting of shock.[21] Overall, the complex interaction of events in this case makes an absolute cause and effect relationship impossible to establish.

4. Conclusion

Mast cells play a central role in many processes including allergy and cancer. The unique elements of this case included a cancer with a surrounding mast cell rich inflammatory infiltrate and peritumoral mast cell degranulation in the setting of an anaphylactic death following multiple bee stings. The exact relationship between these two processes must, however remain conjectural, although a mast cell rich tumor presenting as anaphylaxis is a tantalizing possibility that we could not exclude.

Conflict of interest
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Ethical approval
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Author contribution
The manuscript has been read and approved by all the authors.

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